# Bacteremic Pneumococccal Pneumonia: Current Therapeutic Options

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## ABSTRACT

*Streptococcus pneumoniae* is the major bacterial cause of pneumonia, meningitis and otitis media and continues to be associated with significant morbidity and mortality in individuals both in the developed and developing world. Management of these infections is potentially complicated by the emergence of resistance of this pathogen to many of the commonly used first line antimicrobial agents. A number of significant risk factors exist which predispose to the occurrence of pneumococcal pneumonia, including lifestyle factors, such as exposure to cigarette smoke, as well as underlying medical conditions, such as HIV infection. Several of these predisposing factors also enhance the risk of bacteremia. The initial step in the pathogenesis of pneumococcal infections is the occurrence of nasopharyngeal colonization, which may be followed by invasive disease. The pneumococcus has a myriad of virulence factors that contribute to these processes, including a polysaccharide capsule, various cell surface structures, toxins and adhesins, and the microorganism is also an effective producer of biofilm. Antibiotic resistance is emerging in this microorganism and effects all the various classes of drugs, including the beta-lactams, the macrolides, and the fluoroquinolones. Even multidrug resistance is occurring. PK/PD parameters allow us

to understand the relationship between the presence of antibiotic resistance in the pneumococcus and the outcome of pneumococcal infections treated with the different antibiotic classes. Furthermore, these parameters also allow us to predict which antibiotics are most likely to be effective in the management of pneumococcal infections and the correct dosages to use. Most guidelines for the management of CAP recommend the use of either a beta-lactam/macrolide combination or fluoroquinolone monotherapy for the empiric therapy of more severe hospitalized cases with pneumonia, including the subset of cases with pneumococcal bacteremia. There are a number of adjunctive therapies that have been studied for use in combination with standard antibiotic therapy, in an attempt to decrease the high mortality, of which macrolides in particular, corticosteroids and cyclic AMP-elevating agents appear potentially most useful.

## INTRODUCTION

*Streptococcus pneumoniae* (pneumococcus) remains one of the most important causes of morbidity and mortality in adults and children throughout the world [1]. It is estimated that this microorganism is responsible for more than 100,000,000 cases of ear infections in children, 5,000,000 cases of pneumonia and 100,000 cases of meningitis – the whole being associated with 10,000,000 cases of bacteremia every year [1]. Mortality still remains unacceptably high, this despite all advances in medicine, including the availability of potent antimicrobial therapy, improved medical and nursing care and even the establishment of intensive care unit facilities. Furthermore, management is potentially complicated by the emergence of resistance in the pneumococcus to the commonly used antibiotics. This review will focus on the appropriate management of patients with pneumococcal bacteremia, with particular reference to the antibiotic management of patients with community-acquired pneumonia.

## 1. PNEUMOCOCCAL INFECTION

### 1.1 Epidemiology, risk factors, and prognosis

Interest in pneumococcal infection remains high, which is not surprising considering that this pathogen is the commonest bacterial cause of community-acquired pneumonia, meningitis and otitis media. A number of recent reviews have highlighted the ongoing impact of pneumococcal infections, particularly in the setting of community-acquired pneumonia, and especially in association with bacteremia [2-4]. The incidence of pneumococcal bacteremia has been estimated to be 5.8/100,000 inhabitants/year although a downward trend has been identified recently, most likely as a consequence of effective pneumococcal vaccination [4]. Of the estimated 5,000,000 cases of pneumococcal pneumonia occurring in the USA per year, bacteremia is present in approximately 10-20% of patients, and the mortality remains high even in patients treated appropriately with antibiotics (10-25%) [4]. Almost 10% of infections are complicated by septic metastases to distant organs, causing complications such as meningitis, endocarditis, empyema, peritonitis and various others [4].

The incidence of invasive pneumococcal disease varies substantially and is affected by factors such as socioeconomic status, age, immune status, genetic background and geographical location [3]. Certainly there are a number of well-defined risk factors for

pneumococcal infection and bacteremia in both adults and children [3]. For example, in one study cigarette smoking was found to be one of the strongest independent risk factors for invasive pneumococcal disease (IPD) in immuno-competent, non-elderly adults [5]. Even more recently a comparative study of cases with bacteremic and non-bacteremic pneumococcal pneumonia indicated that smoking was the leading risk factor for pneumonia, and while current smokers had an increased risk of bacteremia, former smokers and COPD patients developed non-bacteremic forms more commonly [6]. Interestingly, although there is some debate about the issue, at least some studies indicate that the outcomes of bacteremic pneumococcal pneumonia in COPD patients are better than expected, with mortality lower in COPD than non-COPD patients [7].

Similarly, HIV infection is a considerable risk factor for pneumococcal infections and especially bacteremic infections, although trends in hospitalizations for IPD appear to be decreasing in countries such as the USA since the introduction of pneumococcal conjugate vaccination in children [8]. Some studies have suggested that there are few differences in the presentation of bacteremic and non-bacteremic pneumococcal pneumonia [9]. However, a more recent study comparing HIV-infected and non-infected patients with bacteremic pneumococcal pneumonia indicated that when adjustments were made for age and severity of illness, HIV-infected cases had a significantly higher 14-day mortality, with a trend to increasing mortality with lower CD4 cell counts [10]. Similarly, a study of CAP occurring in HIV-infected patients indicated that in those patients who were not on antiretroviral therapy, who had positive *S. pneumoniae* antigenuria, there was an increased risk of bacteremia, and that bacteremic patients had a poorer outcome [11].

A number of studies have addressed the question of poor prognostic factors in pneumococcal bacteremia [12,13]. In addition to those factors described above, older age, greater extent of pulmonary consolidation, need for mechanical ventilation/ICU admission, and specific pneumococcal serotypes were associated with a worse outcome [12,13]. The case fatality rate for bacteremic pneumococcal CAP varies in different parts of the world, being 20% in the USA and Spain, 13% in the UK, 8% in Sweden and 6% in Canada, according to one study [12]. Differences in the severity of the disease at presentation, as well as presence and impact on underlying chronic conditions, most likely accounted for these differences. Certainly pneumococcal pneumonia continues to be associated with considerable costs worldwide [14].

## 1.2 Pathogenesis of pneumococcal infections

### *1.2.1 Colonization*

Nasopharyngeal colonization of the non-immune host precedes, and is a prerequisite, for development of invasive disease [15]. Successful colonization necessitates adherence of the pneumococcus to respiratory epithelium, an event which can only be realized if the pathogen survives its early encounters with the innate defense mechanisms of the respiratory tract, most importantly the expulsive actions of the mucociliary escalator. Subversion of the mucociliary escalator is achieved through the coordinated action of an array of protein and non-protein virulence factors. Foremost amongst these is the polysaccharide capsule, which in addition to promoting resistance to opsono-phagocytosis and detection by pattern recognition receptors, enables the pneumococcus to evade entrapment by mucopolysaccharides present in respiratory tract mucus [16]. Several additional virulence factors, most notably

hydrogen peroxide ($H_2O_2$), pneumolysin, and hyaluronidase, act directly on respiratory epithelium, causing ciliary slowing and epithelial damage.

*Toxins*

Through the action of a membrane-bound pyruvate oxidase, the pneumococcus produces prodigious quantities of $H_2O_2$, reaching low millimolar concentrations in bacteriological culture medium [17]. $H_2O_2$ is an indiscriminate, cell-permeable, reactive oxidant, which is toxic for both eukaryotic and prokaryotic cells. Several mechanisms may protect the catalase-negative pneumococcus against the auto-toxic actions of $H_2O_2$. These include exclusion of oxidation-sensitive cysteine residues from exported and cytosolic proteins [18], as well as a possible barrier and/or oxidant-scavenging function of the polysaccharide capsule [19]. Importantly, however, $H_2O_2$ is cytotoxic for ciliated respiratory epithelium, causing dysfunction of the mucociliary escalator [20]. Pneumolysin, which is usually released upon autolysis of the pneumococcus, is considered to be a key protein virulence factor of the pathogen [16,21]. It is a 53kDa protein, which belongs to the family of cholesterol-binding, pore-forming, cytolytic microbial toxins. Like $H_2O_2$, pneumolysin has potent inhibitory effects on the integrity of ciliated respiratory epithelium, causing both ciliary slowing and epithelial damage [22]. These detrimental effects of pneumolysin, and possibly those of $H_2O_2$, are augmented by pneumococcal hyaluronidase, an enzyme which disrupts intercellular adhesion, thereby increasing the exposure of ciliated respiratory epithelium to both cytotoxins [23]. The pneumococcus therefore utilizes a seemingly unique combination of virulence factors *viz* the polysaccharide capsule, $H_2O_2$, pneumolysin and hyaluronidase to inactivate the mucociliary escalator, enabling the pathogen to adhere to the respiratory epithelium.

*Adhesins*

Attachment of the pneumococcus to the epithelium involves an array of bacterial adhesins. In the initial stages, adhesion is likely to be mediated predominantly by the non-protein virulence factor, phosphorylcholine, which interacts with the platelet-activating factor (PAF) receptor on the epithelium [24,25]. The C-polysaccharide of the pneumococcus, as well as some types of capsular polysaccharide, contains phosphorylcholine [26,27]. Phosphorylcholine/PAF receptor-mediated adhesion of the pneumococcus is reinforced by various protein adhesins, including the pneumococcal surface proteins (Psp) A and C (also known as choline-binding protein A – CbpA), and the lipoprotein, pneumococcal surface adhesin (Psa) A, which interact with the epithelial polymeric Ig receptor that normally transports secretory IgA, and E-cadherin, the cell-cell junction protein of respiratory epithelium, respectively [24,28]. Some serotypes also possess pilus-like structures that promote epithelial adhesion via interaction with uncharacterized receptors [29]. A novel protein adhesin has been described recently. This is the 120kDa plasminogen- and fibronectin-binding protein B (Pfb B), which significantly increases the ability of the pneumococcus to adhere to epithelial cells [30]. Unmasking of these various pneumococcal protein adhesins necessitates a reduction in capsule size, with the accompanying risk of increased vulnerability to phagocytosis. This risk is apparently minimized by production of biofilm, a process in which bacterial neuraminidase plays an important role [31,32]. The pneumococcus expresses up to 3 cell surface neuraminidases (Nan A,B,C), which cleave terminal sialic acids from glycan chains on host cells [18], exposing potential binding sites for bacterial adhesins, as well as inducing biofilm formation by free sialic acid [32].

Once colonization is established, several virulence mechanisms are utilized by the pneumococcus to repel innate and adaptive host defenses. These include: i) enzymatic modification of cell-wall peptidoglycans, rendering them resistant to lysozyme present in respiratory secretions [33]; ii) cleavage of secretory IgA by a zinc metalloproteinase [24,25]; iii) interference with activation of the alternative and classical complement pathways by PspA/PspC and pneumolysin respectively [24,34]; and iv) encasement in biofilm as described below [35].

*Biofilm formation*

Biofilm plays an important role in microbial colonization and persistence. It is a hydrated, self-generated polymer matrix in which microbial pathogens are effectively insulated, not only against the cellular and humoral defense mechanisms of the host, but also against antibiotics (recently reviewed by Hall-Stoodley & Stoodley [35]). Concealed in biofilm, either on the epithelial surface, or sequestered intracellularly [35], the pneumococcus can re-emerge at times when host defenses are compromised, as may occur during infection with influenza virus, respiratory syncitial virus, and HIV-1, resulting in invasive disease [36-38].

***1.2 Invasive disease***

As described in a recent review, the progression from colonization of the nasopharynx to invasive infection is likely to involve a complex interplay between the virulence of the infecting strain of the pneumococcus and the efficiency of anti-pneumococcal host defenses [2]. The transition from the relatively innocuous carrier state in the nasopharynx to being a dangerous, invasive pathogen appears to coincide with reversion to higher levels of capsule expression [18], possibly by quorum sensing mechanisms. PspA/PspC – mediated transcytosis of the pathogen across the epithelial barrier via the polymeric Ig receptor enables direct access of the pathogen to the bloodstream and invasion of the central nervous system [24,25]. Spread to the lungs, on the other hand, is most likely to occur by aspiration, with the probability of active infection heightened by preceding respiratory virus infection [36,38]. Influenza virus infection results in prolonged exposure of pulmonary macrophages to interferon-γ, resulting in decreased phagocytic activity of these cells and increased susceptibility to pneumococcal infection [39]. Notwithstanding the involvement of the capsule, pneumolysin is a critical virulence determinant in the pathogenesis of pneumococcal pneumonia [22].

*Pneumolysin*

In addition to its cytolytic activity, pneumolysin, at sub-lytic concentrations, possesses a range of potentially harmful, pro-inflammatory activities, primarily affecting epithelial cells and cells of the innate immune system, especially neutrophils and monocytes/macrophages (reviewed by Feldman & Anderson [2]). These result both from the pore-forming activities of the toxin, leading to influx of extracellular calcium, as well as from its interactions with Toll-like receptor (TLR)-4 [2,41-44]. Activation of intracellular signaling pathways, including those involving p38 and JNK mitogen-activated protein kinases, as well as NFκB, leads to the production of pro-inflammatory cytokines/chemokines including interleukin (IL)-8, monocyte chemotactic protein 1, and tumor necrosis factor (TNF). In the case of neutrophils, interactions of these cells with sub-lethal concentrations of pneumolysin results in exaggerated release of reactive oxygen species, granule proteases, and leukotriene $B_4$

[45,46]. Evidence in support of the involvement of pneumolysin in the pathogenesis of severe pneumococcal pneumonia has largely been derived from murine models of experimental infection. Feldman and colleagues reported that injection of recombinant pneumolysin into the apical lobe bronchus of rats resulted in the development of a severe lobar pneumonia restricted to the apical lobe [22]. More recently, Witzenrath *et al* [47] and Garcia-Suarez *et al* [48] have provided additional interesting insights into the role of pneumolysin in the pathogenesis of acute lung injury (recently reviewed by Feldman and Anderson [2]).

Witzenrath *et al* [47] demonstrated that delivery of recombinant pneumolysin into the airways of mice resulted in increased capillary permeability and severe lung edema, while intravascular administration of the toxin was accompanied by increased pulmonary vascular resistance and lung microvascular permeability. These authors concluded that pneumolysin may play a central role in early-onset acute lung injury by causing impairment of pulmonary microvascular barrier function and severe pulmonary hypertension [47]. They attributed these effects of the toxin, all of which are important features of ARDS, to its direct cytotoxic actions on pulmonary endothelial and epithelial cells, as opposed to pro-inflammatory activities.

Using a murine model of experimental pneumonia in which the mice were infected intranasally with the pneumococcus [48], Garcia-Suarez *et al* reported that pneumolysin was detected in the lungs at sub-lytic concentrations and was located in epithelial cells, macrophages and leukocytes, but not vascular endothelial cells. They concluded that the pro-inflammatory activity of pneumolysin was the major factor in causing tissue damage in their model of pneumococcal pneumonia [48].

Taken together, the findings of these various studies suggest that in severe pneumococcal pneumonia, it is the combined effects of the cytotoxic and pro-inflammatory activities of pneumolysin that lead to acute lung injury and respiratory failure, as well as the epithelial damage that results in translocation of pneumococci from the alveoli to the interstitium and then the bloodstream.

### *1.3 Anti-pneumococcal host defenses*

These have recently been reviewed elsewhere [2]. With respect to innate immunity, the following mechanisms initiate a predominantly neutrophil-mediated inflammatory response which contributes to the early control of colonization: i) the pore-forming interactions of pneumolysin with epithelial cells [42,49]; ii) the interactions of the cell-wall component, lipoteichoic acid, and pneumolysin with TLR-2 and TLR-4 respectively [50]; and iii) the interactions of pneumococcal peptidoglycans with intra-epithelial nucleotide oligomerization domain (Nod) – like receptors, specifically Nod 2 [51].

In the case of adaptive immunity, IgG and secretory IgA antibodies directed against the polysaccharide capsule are generally considered to be the primary determinants of immune-mediated type-specific protection. Antibodies to pneumococcal proteins, particularly PspA, PspC (CbpA) and pneumolysin, also confer protection, which although less efficient, is not serotype restricted [52]. Recently, innate, antibody-independent, anti-pneumococcal host defense mechanisms have been described. These are mediated by $CD4^+$ T cells of the Th1 and Th17 subsets in response to pneumococcal protein antigens [53-55].

## 2. DIAGNOSIS OF PNEUMOCOCCAL INFECTIONS

A large number of microbiological investigations are available, which may be used to try and identify the microbial cause of pneumonia. Among the commonly used standard investigations are sputum Gram's stain and culture and pneumococcal antigen detection, and blood for culture and serological testing. Much less frequently used are invasive techniques, such as fiber-optic bronchoscopy. Yet despite the ready availability of all these investigations, the causative pathogen is only identified, at best, in approximately 50% of cases, with the greatest yield being in the more severely ill cases. Furthermore, it has been suggested that only approximately 20% of cases of pneumococcal pneumonia will be associated with bacteremia, with the isolation of the microorganism on blood culture. A number of new techniques have been introduced, more recently, with the aim of increasing the diagnostic yield for pneumococcal infection, including real-time polymerase chain reaction (RT-PCR) for rapid sputum diagnosis and rapid urine antigen testing (see below). While RT-PCR has not yet been included in most pneumonia treatment guidelines, the rapid urine test has good sensitivity and specificity, but is relatively expensive, and so while it is routinely recommended in some guidelines on the management of pneumonia, other guidelines recommend it be reserved for the more severe infections, such as in cases in the ICU.

### 2.1 Circulating biomarkers in diagnosis and assessment of disease severity and outcome

Measurement of circulating pathogen-derived molecules in combination with host-derived biomarkers of infection and inflammation shows considerable promise in improving the diagnosis of invasive pneumococcal disease, as well as in the assessment of disease severity and prediction of outcome. With respect to the former, the relatively recent acquisition of quantitative real-time PCR procedures for the detection of pneumococcal DNA, usually based on detection of the *lyt A* (autolysin) gene, in blood specimens has been reported to support the diagnosis of CAP caused by the pneumococcus, and may also be a quantitive marker of disease severity [56-59]. In the case of pneumococcal surface antigens, the Binax NOW *Streptococcus pneumoniae* immunochromatographic procedure detects the C-polysaccharide antigen in urine with good sensitivity and high specificity in adult patients with invasive disease [58,60].

Circulating host-derived biomarkers of infection and inflammation, which are reportedly useful as diagnostic and prognostic aids, include C-reactive protein (CRP), procalcitonin (PCT), and possibly soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1). In the case of PCT and CRP, these biomarkers, together with the circulating leukocyte count, have recently been reported to be predictive of 28 day mortality in hospitalized patients with CAP who had not received antibiotic therapy prior to presentation [61]. Measurement of sTREM-1 in bronchoalveolar lavage fluid appears to be useful in distinguishing bacterial/fungal pneumonia from viral pneumonia, atypical pneumonia, tuberculosis and non-infective inflammatory disorders [62,63]. On the other hand, measurement of circulating sTREM-1 has been reported to be of little value in the assessment of etiology, disease severity, and prediction of outcome in patients with CAP [64].

## 3. DRUG RESISTANCE IN *STREPTOCOCCUS PNEUMONIAE*

### 3.1 Prevalence, evolution and mechanisms of antimicrobial resistance

Numerous studies have been conducted over a considerable period of time, which have documented the prevalence and mechanisms of antimicrobial resistance among isolates of *S. pneumoniae.* Antimicrobial resistance among pneumococci has been documented to occur worldwide and to involve the penicillins, macrolides, tetracyclines, trimethoprim, vancomycin and fluoroquinolones, as well as many other agents [3]. Virtually no antibiotic class has remained unaffected. Resistance to penicillin and other beta-lactam agents has been the most discussed resistance problem, but is arguably the least important clinically, since it can usually be overcome by appropriate dosing [65]. The occurrence of drug-resistant pneumococci varies from geographical area to geographical area, and is influenced by antimicrobial prescribing habits in the different regions, and more recently has been impacted on considerably by the introduction of the pneumococcal conjugate vaccine (PCV). The latter has been associated with a significant reduction in invasive disease, as well as in colonization and infection with pneumococcal serotypes contained in the vaccine, many of which harbor resistance genes [56]. However, there has been some increase in infections with replacement serotypes, many of which now also carry antibiotic resistance.

#### *3.1.1 Penicillin resistance*

Penicillin resistance occurs as a consequence of alterations in one or more of the cell wall penicillin-binding proteins, which catalyze bacterial cell-wall production, and this affects the affinity of the whole class of beta-lactam antibiotics for these binding proteins [65,66]. This mechanism of resistance can be overcome if the concentration of the beta-lactam agent at the site of infection is high enough which allows for binding to, and inhibition of, the enzyme [65,66]. Prior antibiotic use is the prime driver of drug-resistant pneumococcal infections [67]. Penicillin-resistant pneumococci appeared in a few geographic areas, such as Australia, Spain and South Africa, in the 1970s, but subsequently spread rapidly across the world, particularly during the 1980s, 1990s and 2000s [67,68]. For example, in one study the proportion of resistant pneumococcal isolates increased nearly 30-fold during the period 1993-2004 [65]. Rates of penicillin resistance exceeding 50% occur in certain areas of the world, such as Spain and Asia, but remain low in other regions (<5%), such as Finland and Sweden [66,67]. Because such significant differences occur in different parts of the world, it is important to consider regional data when making decisions regarding antibiotic treatment [66].

One significant change that has occurred with regard to the evaluation of penicillin resistance has been the redefining of the penicillin breakpoints for resistance in the case of non-meningeal infections. For many years penicillin susceptibility for all infections has been defined in pneumococcal strains as an MIC < 0.06 μg/ml, intermediate resistance as an MIC of 0.12-1 μg/ml, and resistance as an MIC of 2 μg/ml [65]. In 2008, the CLSI changed the penicillin breakpoints for non-meningeal infections (such as CAP) treated with intravenous therapy as follows; susceptible (≤ 2 μg/ml), intermediate (4 μg/ml) and resistant (≥ 8 μg/ml) [69]. For non-meningeal infections treated with oral penicillin V, the old breakpoints still remain valid. Using contemporary microbiological data, up to 95% of pneumococcal strains worldwide are expected to have MICs in the susceptible range for intravenous high dose penicillin therapy [66]. Furthermore, the occurrence of highly penicillin-resistant strains with

MICs ≥ 8 μg/ml is currently rare. Among other beta-lactams, such as the cephalosporins, the MIC distribution varies for the different agents, with antibiotics such as cefuroxime, cefotaxime and ceftriaxone being more active against the pneumococcus, although their activity has changed over the years [65].

### *3.1.2 Macrolide resistance*

Macrolide resistance is most commonly mediated by one of two main mechanisms, which sometimes occur concomitantly. The first of these occurs as a result of expression of the *mefA* gene, resulting in the M phenotype, which is associated with an efflux pump that removes macrolides from within the cell [65]. The second occurs as a consequence of the expression of the *ermB* gene, associated with the MLSB phenotype, which is associated with expression of an erythromycin-ribosomal dimethylase that blocks the binding of macrolides to the ribosomal target [65]. The former is associated with more moderate resistance, and continued susceptibility to the lincosamides (and therefore clindamycin). The latter is associated with highly resistant strains, and with this mechanism, there is also a block in the binding of lincosamides and streptogramin B agents [65]. The prevalence of the different macrolide resistance mechanisms varies in different parts of the world, but globally the latter is said to account for 55% overall, followed by the former in 30.6% and both in 12% [66]. Both mechanisms have been associated with failure of macrolide therapy, arguing against the use of macrolide monotherapy in areas of high prevalence of resistance [68]. The worldwide prevalence of macrolide resistance escalated at the same time as penicillin resistance, especially during the 1990s, and correlated, not surprisingly, with the use of macrolides [67,68]. Dual non-susceptibility to penicillin and macrolides has also been observed [68]. By the mid 1990s macrolide resistance exceeded 20% in many countries, but similarly to that of penicillin resistance varies by region (from < 3% to > 70%) [67]. Clonal spread is an important vehicle for the spread of macrolide resistance [67].

### *3.1.3 Fluoroquinolone resistance*

Fluoroquinolone resistance develops as a consequence of chromosomal mutations in the quinolone resistance determining region (QRDR) of the pneumococcus, involving the *parC* gene for topoisomerase IV and the *gyrA* gene of the DNA gyrase [65]. Mutations in one region may result in low level resistance, while dual mutations confer high level resistance [65]. Significant fluoroquinolone resistance remains uncommon, being less than 2% in most countries but is of potential concern because of widespread use of these agents in various different settings [65,67].

### *3.1.4 Multidrug resistance*

Furthermore, even multi-drug resistant strains of pneumococci have emerged (resistance to 3 or more different classes of antibiotics) and in one study the frequency of such strains increased considerably from 9.1% in 1995 to 20% in 2005 [66].

## 3.2 Impact of antimicrobial resistance on outcome of pneumococcal infections

While many studies have investigated the prevalence and mechanisms of pneumococcal resistance, much less attention has been focused on the true impact of antimicrobial resistance on the outcome of pneumococcal infections, treated with standard antimicrobial agents. In many studies, current levels of antibiotic resistance have been shown to have very limited impact on the clinical outcomes of patients with pneumococcal CAP, particularly with regard to penicillin and other beta-lactam

agents; yet antimicrobial prescribing habits have changed because of concerns about resistance [70-72]. There is also mounting evidence that support relatively simple strategies to overcome the impact of resistance, such as using high doses of antimicrobial agents, using more active agents within a specific class of antibiotics or switching to another class of antibiotic, particularly in cases at increased risk of infection with highly resistant pneumococci [73].

### *3.2.1 Beta-lactam resistance*

A large, multicentre, prospective, international, observational study investigated 844 hospitalized patients with *S. pneumoniae* bacteremia [74]. The investigators were specifically chosen since they worked in institutions in cities or countries that had previously been reported to have a high prevalence of drug non-susceptible pneumococci. Overall 15% of isolates were of intermediate susceptibility to penicillin (MIC 0.12-1 µg/ml) and 9.6% were highly resistant (MIC > 2 µg/ml). The impact of concordant antibiotic therapy (receipt of one antibiotic with high *in vitro* activity against the pneumococcal isolate) versus discordant therapy (antibiotic inactive *in vitro*), on 14-day mortality were assessed. Discordant therapy with penicillins, cefotaxime, and ceftriaxone (but not cefuroxime at 750 mg three times daily – see below) did not result in a higher mortality. Neither was there a difference in time to defervescence or frequency of suppurative complications. An additional study indicated that only discordant therapy with beta-lactam agents that had poor anti-pneumococcal activity impacted on outcome, but not penicillins or broad spectrum beta-lactams [75]. Furthermore, although there are some studies indicating possible impact of beta-lactam resistance on outcome, a critical review of the literature among patients with pneumococcal pneumonia, both with and without bacteremia, revealed only one single case of a documented microbiological failure of parenteral penicillin-class antibiotics, in a patient with an empyema, into which antibiotics are known to penetrate poorly [76]. Some have therefore suggested that even penicillin appears to be adequate and effective, when administered in adequate dose and frequency, for the treatment of pneumococcal pneumonia [77].

### *3.2.2 Macrolide resistance*

The same is not quite true for the macrolides and fluoroquinolones [73,78,79]. With regard to the macrolides, Lonks and colleagues [78] conducted a matched case control study of patients with bacteremic pneumococcal infections to determine whether breakthrough bacteremia occurring during macrolide treatment was related to macrolide susceptibility of the pneumococcal isolates. Cases were patients with patients with pneumococcal bacteremia and isolates that were either resistant or intermediately resistant to erythromycin, whereas controls were age, gender, location and year matched cases in whom the isolates were susceptible to erythromycin. Excluding meningitis cases, 18 of the cases (24%) and none of the 136 matched controls were taking a macrolide when blood was taken for the culture ($p=0.00000012$). A similar result was seen even in cases infected with isolates carrying the low-level resistant M phenotype, thus suggesting that both efflux and methylation mechanisms of resistance may be clinically relevant and associated with breakthrough bacteremias in patients being treated with macrolides [78-80]. A number of additional cases of macrolide treatment failures have been reported, although these are few in number compared to the overall number of pneumococcal cases, and specifically cases due to macrolide resistant isolates seen every year [73].

### *3.2.3 Fluoroquinolone resistance*

Similarly, fluoroquinolone treatment failures have also been documented in patients infected with fluoroquinolone-resistant *S. pneumoniae* [73]. All these cases were treated with either ciprofloxacin, known to be poorly active against the pneumococcus or levofloxacin given as 500mg daily, a dose that is not considered to be optimum based on a current understanding of optimal PK/PD parameters (see below).

## 3.3 Antibiotic therapy of drug resistant infections

In a number of review articles, the evidence in the literature for the impact of antimicrobial resistance on the outcome of pneumococcal infections, treated with various different antibiotic classes has been evaluated and firm recommendations made with regard to specific therapy [81-84]. These are described more fully below. In the first instance it is important to note that it is not only the specific antibiotic class itself that is important in the outcome of an infection, but also the dose that is given, the route it is administered, the timeliness of antibiotic administration from the time of presentation of the patient with the infection, and the pharmacodynamic (PD)/pharmacokinetic (PK) properties of the agent administered (see below).

In general, certainly with regard to the use of parenteral beta-lactam agents for the treatment of pneumococcal pneumonia, current prevalence and levels of penicillin resistance are such that either penicillin itself or the aminopenicillins could be used in standard doses. In the case of infections with strains of intermediate resistance higher drug dosages are recommended. In the case of high level resistance, alternative agents, such as the third generation cephalosporins (e.g. ceftriaxone, cefotaxime) or the respiratory fluoroquinolones (e.g. levofloxacin, moxifloxacin, gemifloxacin), should be used.

With regard to the macrolides (including the azalide agent, azithromycin), these agents are not recommended for use as monotherapy in areas where there is a high prevalence of macrolide-resistant pneumococcal infections. However, in the case of a young, previously healthy individual, who has not had a recent course of antibiotics and is presenting with a mild pneumonia that is to be treated at home, macrolide monotherapy may be suitable, since in this situation macrolide resistance is much less likely to occur. Furthermore, macrolides are still recommended as appropriate therapy for so-called “atypical” infections and also as part of combination therapy. The latter (i.e. beta-lactam/macrolide combination) is considered a suitable therapy for the more severe, hospitalized patient with pneumococcal CAP, including the subset of cases with pneumococcal bacteremia. An alternative choice for the latter is fluoroquinolone monotherapy, although it is often recommended that these agents are reserved for specific cases in order to prevent rapid development of antibiotic resistance.

With regard to the fluoroquinolones, while the presence of two significant mutations in the QRDR is associated with fluoroquinolone resistance, such that these agents are not suitable for therapy, this occurrence is still very uncommon worldwide. However, what is not fully appreciated is that isolates with single-step mutations do occur, may well test as susceptible in the laboratory, and resistance may subsequently occur during fluoroquinolone therapy due to the spontaneous occurrence of a second mutation. Furthermore, the prevalence of these single-step mutations in many areas of the world is uncertain. When used, fluoroquinolones need to be given in appropriate doses that may limit the emergence of these mutations (see below).

### *3.4 Pharmacokinetic/Pharmacodynamic parameters and antibiotic choice and dosing*

The use of drug pharmacokinetic (PK)/pharmacodynamic (PD) principles is the new pharmacological science that enables us to understand the relationship between drug dosing and its likely efficacy, and is particularly useful in the era of emerging antibiotic resistance. This has been discussed in a number of review articles and is described more fully below [85-87]. With the use of the PK parameters of drug serum concentration over time and area under the concentration curve and integrating these with the MIC of the microorganism one could predict the likelihood of clinical success and pathogen eradication. Use of PK/PD parameters is also helpful for preventing selection and spread of resistant microorganisms and has lead to the development of the concept of the mutant selection concentration (MPC), which is the lowest concentration of the antimicrobial that prevents selection of resistant bacteria from high inocula of organisms [88].

Beta-lactam antibiotics and the macrolides (but not the azalides) are time-dependent antimicrobials and the major PK/PD parameter correlating with the outcome is the so-called time above MIC (T > MIC); the serum level of the antibiotic needs to be above the MIC of the microorganism for 40-50% of the dosing interval for likely success (Figure 1). Using standard dosing regimens of the various drugs and comparing these to the MIC(s) of individual pathogens or a collection of strains, one can determine if a T>MIC of 40-50% of the dosing interval is achieved (equivalent to the breakpoint of the pathogen being below the resistance breakpoint) and therefore whether use of the drug is likely to be associated with clinical success. In the example given in Figure 1, this would have been successfully achieved with drug A, but not with drug B. It is for this reason that there is continuous ongoing success with the use of the penicillins and aminopenicillins in the management of pneumococcal infections in most areas of the world, since given current levels of pneumococcal penicillin resistance worldwide, together with appropriate increased dosing a T > MIC of 40-50% or greater is readily achieved. In the case of cefuroxime, the T>MIC with standard dosing is borderline, particularly in the presence of slightly elevated MICs, but sufficient with higher dosing (e.g. parenteral cefuroxime 750 mg three times daily has been associated with treatment failures but not 1500 mg three times daily [74]). In the case of the macrolides, a T >MIC of 40-50% is achieved with susceptible isolates, but not with macrolide- resistant isolates, in which macrolide monotherapy, in any dose, is therefore not recommended. These agents may still be used as part of combination therapy (see elsewhere).

In the case of the fluoroquinolones, which kill pathogens by a concentration dependent mechanism, the major PK/PD parameter predictive of likely outcome is the so-called AUIC (area under the inhibitory curve = the area under the serum drug concentration curve to MIC ratio) (Figure 2). While there are differences in the values predictive for likely failure or success of fluoroquinolone therapy in immunocompetent versus immunosuppressed individuals, in milder or more severe infections and for gram-negative versus Gram-positive pathogens, a number of studies suggest (as do many investigators) that the appropriate AUIC value to aim for in both Gram-positive and Gram-negative pathogens should be similar (> 100 or even > 125) [89]. This is not achieved with either oral or parenteral doses of levofloxacin of 500mg daily, but is achieved with 750 mg daily, which is the currently recommended dose

for this fluoroquinolone and is also achieved with standard doses of moxifloxacin [90], and gemifloxacin.

## 4. ANTIBIOTIC THERAPY OF PNEUMOCOCCAL PNEUMONIA

### 4.1 Early initiation of antibiotic therapy

A number of studies have suggested that there is a significant and causal relationship between timing of initial antibiotic therapy and improved outcome (length of hospital stay and mortality) in patients with CAP [91]. This association appeared to be particularly strong among older patients who had not yet received antibiotic prior to arriving at the hospital. However, two recent studies among patients with bacteremic pneumococcal CAP have indicated that administration of adequate antimicrobial therapy within 4 hours of arrival at hospital was a critical determinant of survival in these patients [92,93]. In the former study, 363 patients were studied. The median time to first administration of antibiotics was 2.8 hours. Overall 66% of patients received at least one active antibiotic within 4 hours, 82% within 8 hours and 94% within 24 hours. Receipt of at least one active antibiotic was associated with a reduced mortality (OR 0.47 [95% CI 0.2-1.0]; p=0.04) and shortened length of stay (OR 0.77 [95% CI 0.60-1.0]; p=0.03). In the latter study, a time period of > 4 hours to the first administration of adequate antibiotics was independently associated with in-hospital mortality [93]. As a result of the many studies, time to first antibiotic administration in patients presenting to hospital has been an audited performance measure for CAP for many years [94-97]. However, there have been some concerns about the recommendation of antibiotic administration within 4 hours of presentation of patients with suspected CAP. Firstly, this would necessitate the treatment of at least some patients, such as those presenting in an atypical manner, before a firm diagnosis of CAP is made [95,96]. Secondly, in some studies that have shown benefit of early antibiotic administration (within 4 hours) on outcome, the factors associated with antibiotic delay were conditions such as altered mental state, absence of fever, absence of hypoxia, and increasing age, many of which, in themselves, may impact negatively on mortality [95,96]. The IDSA/ATS Pneumonia Guideline now recommends that the first antibiotics be given in the emergency department, rather than assigning a specific time point to this process [98].

### 4.2 Combination antibiotic therapy

A myriad of studies in patients with CAP, both of all-cause (including cases of pneumococcal infections), as well as those due to *S. pneumoniae* alone (including the subset of patients with pneumococcal bacteremia) have indicated that combination antibiotic therapy, most commonly the addition of a macrolide to standard beta-lactam antibiotic therapy, is associated with improved outcomes [99-103](Table 1). Furthermore, the benefits of adding a macrolide to therapy in patients with CAP extended to cases with severe sepsis, as well as to intubated patients [104,105]. These findings need to be counterbalanced by additional studies not showing such benefits, or showing benefits in only selected subgroups of patients [106-109], as well prospective, randomized investigations suggesting that fluoroquinolone monotherapy may be at least as effective as combination therapy [110,111]. This situation is further confounded by other studies indicating that the use of beta-lactam/fluoroquinolone combination in patients with severe pneumonia of all-cause, may be associated with increased short term mortality compared with that of other, guideline compliant, therapy [112]. As a consequence of these various studies, and despite the apparent contradictions, most

guidelines, such as the IDSA/ATS guideline [98] recommend the use of a beta-lactam/macrolide combination or fluoroquinolone monotherapy for the treatment of sicker, hospitalized patients with CAP, including the sub-set of cases with pneumococcal bacteremia [98,113]. It has been suggested that the major discriminatory factor that may influence the choice between fluoroquinolone monotherapy or beta-lactam/macrolide combination therapy is the history of recent prior antibiotic therapy in the patient [98]. Another factor that may be of influence is a history of antibiotic allergy in the patient. One additional question that has been raised, is how long the benefit from combination therapy lasts and therefore how long combination antibiotic therapy should be continued. In the study by Baddour and colleagues [102], potential benefit of combination antibiotic therapy was evaluated for both day 1 and day 3 and was found to be present for both. It is usually recommended that combination therapy be continued for at least 3 days. Another consideration is what to step down to, or switch to (see below), when intravenous combination therapy with a beta-lactam and a macrolide has been used initially. It has been suggested that it may be to either class of drug, including a macrolide alone, provided the patients are not infected with drug resistant *S. pneumoniae* or Gram-negative enteric pathogens[98].

The exact reason(s) for and/or mechanism(s) of benefit of the addition of macrolides is uncertain, but may be multifactorial (see below and Table 2 and 3). In the study by Gamacho-Montero and colleagues described previously [93], combination therapy was protective against delayed adequate therapy (aHR 0.53 [95% CI 0.29-0.95]; p=0.033), the latter potentially associated with a poorer outcome, as described above. Another suggestion is that the addition of macrolides would cover for so-called "atypical pathogens". Interestingly, Metersky and colleagues [114] addressed the question of whether adding agents active against "atypical pathogens" (namely macrolides, fluoroquinolones or tetracycline) was associated with better outcome in patients with bacteremic pneumonia. Their study indicated that while the initial use of an antibiotic active against atypical pathogens was independently associated with decreased risk of 30-day mortality and hospital admission within 30 days of discharge, this benefit was only associated with the use of macrolides and not fluoroquinolones or tetracyclines. There is additional evidence to suggest that the beneficial effects of macrolides may go beyond their primary antimicrobial activity. For example, in the study by Restrepo and colleagues, of patients with severe pneumonia and sepsis, benefit was seen with the addition of macrolides even in the presence of macrolide-resistant microorganisms [104].

A further mechanism may relate to anti-inflammatory effects combination antibiotic therapy has on cytokine release. In severe pneumococcal pneumonia, acute phase proteins and various cytokine levels are raised and the longer the time from onset of pneumonia symptoms to hospital presentation, the higher these values are [115]. Furthermore, levels of TNF correlate with levels of interleukin (IL)-1β, IL-6, and IL-8 and are associated with the presence of bacteremia, initial blood pressure < 90mmHg, and with lower oxygen concentration on admission, all potential indicators of severity. In subsequent studies high IL-6 levels were associated with the worst outcomes in patients with pneumococcal pneumonia and initial combination antibiotic therapy produced a faster decrease in IL-6 levels than monotherapy [116]. These and a range of other, non-antimicrobial, anti-inflammatory, immunomodulatory effects of macrolides, are believed by many, to underlie the benefits achieved with combination therapy [117,118].

Guideline compliant therapy, such as is indicated in the IDSA/ATS guideline, with the use of a beta-lactam macrolide combination or fluoroquinolone monotherapy, has been studied and been shown to be associated with lower mortality, decreased complication risk, decreased time to clinical stability and associated duration of parenteral therapy, decreased length of hospital stay and therefore overall resource utilization in adult patients, including the elderly, with CAP [119,120]. Furthermore, the use of a macrolide/beta-lactam combination or fluoroquinolone monotherapy in patients hospitalized with CAP has been included as one of the quality measures in the treatment of patients with CAP [97]. The ultimate choice of the antibiotic regimen for the individual patient (i.e. whether beta-lactam-macrolide combination or fluoroquinolone monotherapy) would depend on a number of host factors, including an appreciation of what antibiotics the patient has had in the recent past (preceding 90 days), the presence of allergy to a particular class of antibiotics and/or other factors that may preclude the use of certain agents. The reason that preceding antibiotic use should be taken into consideration is that it increases the likelihood of the current infection being due to microorganisms that are resistant to that previously used class of antibiotics[98].

**4.3 Switch and de-escalation therapy**

For those patients with CAP that are admitted to hospital, most guidelines recommend that patients should be switched from intravenous to oral antibiotic therapy ("switch therapy") as soon as they are haemodynamically stable, are clinically improving, are able to ingest oral medications and have no gastrointestinal dysfunction [98]. Ramirez *et al*., established criteria for early switch therapy, which are commonly used [121,122]. In the IDSA/ATS CAP guideline [98], the criteria indicated for clinical stability include a temperature < 37.8$^{o}$C, heart rate < 100 beats/min, respiratory rate < 24 breaths/min, systolic blood pressure > 90mm Hg, arterial oxygen saturation > 90% or $PO_2$ > 60 mmHg on room air, in a patient who is able to maintain oral intake and has a normal mental status. Subsequent studies have suggested that even more liberal criteria are adequate for switch to oral therapy.

Ramirez and colleagues studied early switch therapy in a number of clinical situations, including both CAP of all cause, as well bacteremic community-acquired *Streptococcus pneumoniae* pneumonia [123-125]. In the earlier study by Ramirez and colleagues [124], patients with pneumococcal bacteremia were less likely to reach clinical stability and become candidates for switch therapy than general populations of CAP patients, and there was also a delay in time to reach clinical stability. However, in the absence of meningitis or endocarditis, bacteremic patients reaching clinical stability could safely be stepped down to oral therapy [124]. This study was superseded by a more recent study from this research group, which was a secondary analysis of the Community-Acquired Pneumonia Organization (CAPO) database of hospitalized patients with CAP and pneumococcal bacteremia (124 cases)[125]. Initial association between pneumococcal bacteremia and poorer outcomes became insignificant when adjusting for other co-variates. Thus the multivariate regression analysis revealed no association between bacteremic CAP and time to clinical stability (HR 0.87 [95% CI 0.7-1.1]; p=0.25), length of hospital stay (HR 1.14 [95% CI 0.91-1.43]; p=0.25), all-cause mortality (OR 0.68 [95% CI 0.36-1.3]; p=0.25), or CAP-related mortality (OR 0.86 [95% CI 0.35-2.06]; p=0.73). Clearly the factors related to severity of illness were confounders for the association between pneumococcal bacteremia and poor

outcome, explaining the earlier findings. The authors concluded that pneumococcal bacteremia itself was not a contraindication to deescalating therapy in clinically stable patients.
However, despite these findings, a more recent study has documented that there is evidence in the literature of considerable variability in the practice of early switch therapy for patients with CAP [126]. This needs to be addressed since the advantages of early switch therapy are that patients are converted from intravenous to oral therapy earlier and usually discharged from hospital sooner. Since duration of parenteral antibiotic therapy is often the primary factor affecting length of hospital stay (LOS), and LOS is the major determinant of costs of therapy, early switch therapy and early discharge may be associated with significant cost saving in the management of patients with CAP.

## 5. ADJUNCTIVE THERAPIES FOR PNEUMOCOCCAL CAP

As mentioned above, β-lactam antimicrobial agents are the cornerstone of therapy of pneumococcal pneumonia. Nonetheless, considerable effort continues to be directed at the identification of adjunctive therapies which attenuate adverse inflammatory responses, or, alternatively, augment host defenses. Foremost among the former are macrolide antibiotics, largely because of their secondary anti-inflammatory properties, while corticosteroids, and possibly cyclic AMP-elevating agents show promise. The latter group includes passive immunotherapeutic agents such as hyperimmune serum, intravenous gammaglobulin, and monoclonal antibodies. The therapeutic potential of inhibitors of intravascular coagulation, exogenous surfactant, and statins has recently been reviewed in detail elsewhere [127].

### 5.1 Macrolides

While macrolides are more usually considered simply as antimicrobial agents that have a role in the antibiotic therapy of pneumococcal CAP, the mechanism(s) underlying their benefit may not relate directly to their antimicrobial activity but rather to their additional activities (Table 3). As such, although not yet conclusively proven, inclusion of a macrolide may rather represent the most compelling adjunctive strategy in the treatment of severe pneumococcal pneumonia [114,128]. Macrolides possess a combination of properties, both antimicrobial and non-antimicrobial, which are likely to underpin their apparent usefulness as adjuncts to β-lactams in CAP. Benefit related to antimicrobial activity appears to result from the bacterostatic and protein synthesis inhibitory effects of these agents [114]. The benefits of non-antimicrobial activity are largely attributable to the immunomodulatory/ anti-inflammatory activities of macrolides [128,129](Table 3).

#### *5.1.1 Indirect anti-inflammatory activity of macrolides*

Bactericidal antibiotics, including β-lactams and fluoroquinolones, exacerbate pathogen-directed inflammatory responses as a consequence of the release of pro-inflammatory intracellular toxins and cell wall components from distintegrating bacteria, which is likely to be most evident in the clinical setting of high bacterial loads. In the case of the pneumococcus, release of lipoteichoic acid and peptidoglycan from the cell-wall may exacerbate the inflammatory response via interactions with TLR-2 and Nod 2 respectively, which is intensified by the pore-forming, TLR-4-binding, and complement-activating effects of pneumolysin. On the

other hand, the actions of inhibitors of bacterial protein synthesis are more subtle and controlled. These antibiotics, especially macrolides and macrolide-like agents, subdue and weaken their target pathogens by attenuating the production of pro-inflammatory protein toxins and other virulence factors such as adhesins, quorum sensors, and biofilm. Importantly, these activities of macrolides are not only evident with macrolide-susceptible strains of the pneumococcus, but also with macrolide-resistant strains, as well as organisms with innate resistance such as *Escherichia coli* and *Pseudomonas aeruginosa* [130-134]. In the case of the pneumococcus, we have found macrolides to be extremely effective inhibitors of the production of pneumolysin, even in the setting of macrolide resistance [131,132]. The importance of this is that pneumolysin is considered by many to be the most important virulence factor of the pneumococcus and plays a major role in the pathogenesis of severe pneumococcal pneumonia (see above).

The distinction between beta-lactams and macrolide/macrolide-like agents with respect to pro-inflammatory activity has been demonstrated in several models of experimental infection, including a recent study using a murine model of secondary, influenza-associated pneumococcal pneumonia. In this study, the lowest survival rate in antibiotic-treated animals was observed in those treated with ampicillin only, with the highest rates being observed in those treated with azithromycin or clindamycin only, or in combination with ampicillin [135]. Improved survival in the groups treated with azithromycin/clindamycin was associated with an attenuated inflammatory response, demonstrating that macrolides counteract the pathogen-directed pro-inflammatory activity of β-lactams.

### *5.1.2 Direct anti-inflammatory activities of macrolides*

Macrolides have extremely high levels of tissue penetration and are highly concentrated by epithelial cells and cells of the innate immune system. These agents appear to be particularly effective in controlling neutrophil-mediated inflammation, which may explain their efficacy in the therapy of acute and chronic respiratory disorders such as chronic obstructive pulmonary disease, panbronchiolitis, obliterative bronchiolitis and cystic fibrosis in which the neutrophil appears to be the primary offender (reviewed by Feldman & Anderson [129]). Several mechanisms of anti-inflammatory activity, possibly interactive, have been attributed to macrolides. These include membrane-stabilizing activity [136], as well as inhibition of synthesis of the potent neutrophil chemoattractant, IL-8, by a variety of structural and inflammatory cells, including bronchial epithelial cells and monocytes (reviewed in Feldman & Anderson, 2005 [137]). This latter activity results from macrolide-mediated interference with intracellular signaling mechanisms which converge on transcriptional activation of IL-8 gene expression [138-140].

In summary, the unusual combination of excellent cell and tissue penetration, antimicrobial, and anti-inflammatory activities appear to account for the apparent efficacy of macrolides as adjuncts to β-lactams in the treatment of severe pneumococcal pneumonia, as opposed to activity against atypical pathogens [114].

## 5.2 Corticosteroids

Adjunctive corticosteroids have become routine treatment in the clinical management of adults with bacterial meningitis, significantly reducing hearing loss and neurological sequelae, as well as mortality in pneumococcal meningitis [141,142]. To

date, however, there are no published studies which have specifically addressed the adjunctive potential of corticosteroids in severe pneumococcal pneumonia. Several relatively small studies, most recently those reported by Confalonieri *et al* [143] and Garcia-Vidal [144], have reported benefit of early administration of systemic corticosteroids to hospitalized patients with severe CAP. Clinical benefit manifested as significant improvements in the $Pao_2/Fio_2$ ratio and chest radiograph, as well as reductions in the multiple organ dysfunction score and mortality. However, in a recent and much larger randomized, double-blinded clinical trial, Snijders *et al* [145] did not detect beneficial effects of early administration of corticosteroids (systemic or oral) on outcome of patients with CAP. Although the authors conceded that possible benefit of adjunctive corticosteroids in more severely ill patients could not be excluded, it is noteworthy that Sprung *et al* [146] also failed to detect benefit of intravenous corticosteroids in patients with septic shock, irrespective of the response to corticotrophin. Hydrocortisone therapy did, however, hasten reversal of shock, but this was negated by the higher frequency of superinfection, including new sepsis and shock, in the steroid-treated group [146].

On the basis of recent evidence, the role of corticosteroids in the adjunctive therapy of severe pneumococcal pneumonia remains uncertain. It is, however, noteworthy that corticosteroids, unlike macrolides, are relatively ineffective in controlling the harmful pro-inflammatory activities of neutrophils [147], suggesting that these agents may be most effective when they are used in combination. In this respect, it may be meaningful that "the use of macrolides was discouraged because of their immunodulating effect" in the study reported by Snijders *et al* [145], while Confalonieri *et al* [143] "followed the 1993 American Thoracic Society Guidelines for the initial management of adults with community acquired pneumonia," which advocates: i) " a second- or third-generation cephalosporin *or* beta-lactam/beta-lactamase inhibitor +/- macrolide for hospitalized patients with CAP;" and ii) a "macrolide + third-generation cephalosporin with anti-*Pseudomonas* activity *or* other anti-pseudomonal agents such as imipenem/cilastatin, ciprofloxacin for severe hospitalized patients with community-acquired pneumonia" [148]. Antibiotic usage was not specified in the reports authored by Garcia-Vidal *et al* [144] and Sprung *et al* [146].

### 5.3 Cyclic Adenosine Mlonophosphate-elevating agents

Cyclic AMP possesses broad-ranging, anti-inflammatory activities affecting various types of immune and inflammatory cells and their pro-inflammatory mediators, and has been described recently as the "master regulator of innate immune cell function" [149]. The molecular/biochemical basis of the anti-inflammatory activity of cAMP largely involves activation of cAMP–dependent protein kinase (PKA). This kinase, in turn, mediates the removal/exclusion of $Ca^{2+}$ from the cytosol of activated immune and inflammatory cells by several interactive mechanisms [150], and also antagonizes the interaction of NFκB with the transcriptional cofactor, cAMP response element binding- protein (CREB), a critical event in activation of histone deacetylase and gene expression [151]. Cyclic AMP-mediated clearance of cytosolic $Ca^{2+}$ effectively down-regulates the $Ca^{2+}$-dependent pro-inflammatory activities of neutrophils, including the generation of reactive oxidant species and leukotriene $(LT)B_4$, expression of the β2-integrin, CR3, and release of granule proteases [152-154]. Antagonism of NFκB, on the other hand, results in decreased synthesis of pro-inflammatory cytokines, especially IL-8 and TNF, by other cell types such as monocytes/macrophages and epithelial cells [151].

Although largely untested in severe pneumococcal pneumonia in either the clinical or experimental settings, sepsis has been identified as being a potential area for the therapeutic application of cAMP-elevating pharmacological agents, and several experimental studies appear to bear this out. Importantly, human leukocytes possess G-protein-coupled adenosine $A2_A$, β2-adrenergic, and EP receptors, all of which are linked to adenylyl cyclase; they also possess cyclic nucleotide phosphodiesterase (PDE) enzymes (reviewed by Tintinger *et al* [150]).

In patients with severe sepsis/septic shock, intracellular cAMP levels are significantly decreased in blood mononuclear leukocytes, which is associated with impairment of both β-adrenergic receptor-dependent and –independent activation of adenylyl cyclase, and an extended post-receptor defect of β-adrenergic signal transduction [155]. Decreased intracellular cAMP is likely to result in hyperreactivity of immune and inflammatory responses. In addition, defective β-adrenergic signaling in the cardiovascular system in humans appears to underpin the myocardial hyperresponsiveness to catecholamines/ myocardial depression that occurs in sepsis [156,157].

Notwithstanding the use of inotropes, strategies to augment intracellular cAMP in the acute clinical setting are, realistically, limited to non-methylxanthine, non-specific inhibitors of PDEs. This is because leukocytes and structural cells vary with respect to their expression of the various PDE subtypes, clearly restricting the use of selective inhibitors, while methylxanthines are potentially toxic. Three agents, all of which are non-methylxanthine, non-specific PDE inhibitors, merit serious consideration as potential adjuncts in the therapy of severe pneumococcal disease and sepsis/septic shock. These are pentoxifylline, which has already shown promise in neonatal sepsis [158-160], as well as ibudilast [161] and montelukast [153]. Neither ibudilast nor montelukast has been evaluated in patients with severe CAP/Sepsis. However, both agents combine cysteinyl leukotriene receptor antagonistic activity with non-specific PDE inhibitory activity [153,161], making them particularly attractive contenders for evaluation in this setting.

**5.4 Antibody administration**

In his recent review Wunderink describes the small reduction in mortality (~10%) which was associated with the passive administration of hyperimmune serum to patients with pneumococcal pneumonia in the pre-antibiotic era, while the benefit, if any, of administration of intravenous gammaglobulin to patients with CAP remains unproven [127]. Such a study was conducted several years ago by one of us, among patients with suspected pneumococcal CAP, admitted to an intensive care unit in Johannesburg, South Africa (Feldman C, personal communication). This was a prospective, randomized, double blind, placebo-controlled study using a hyperimmune pneumococcal gammaglobulin preparation containing antibodies to 14 pneumococcal serovars/groups administered in a dose of 400mg/kg, or matching placebo, which was administered to all study patients within 24 hours of admission to hospital/ICU. All patients received, in addition, identical standard treatment for community-acquired pneumonia, including antibiotics, as per the ICU protocol. An attempt was made to include only cases with pneumococcal CAP, using strict microbiological criteria, and additional laboratory testing included sputum Gram's stain and culture, blood cultures and sputum and blood countercurrent pneumococcal

immunoelectrophoresis. Initially 12 cases were enrolled in the study, of which 9 were subsequently confirmed to have pneumococcal infection. Of these 9 pneumococcal cases, four of the six serum-treated patients died, whereas all three placebo treated patients survived (p=0.12). A further three cases of suspected pneumococcal pneumonia, not subsequently confirmed as having pneumococcal infection, had been enrolled, 1 of whom had received serum and subsequently died. The other two survived. Thus a total of five of 12 patients died, all of whom had received serum, and 7 survived, two of whom had received serum (p=0.027). On the basis of these differences in mortality the study was stopped as was a requirement of the regulatory authorities in South Africa.

An alternative, experimental approach described by Garcia-Suarez *et al* (2004)[162] was based on the intravenous administration of monoclonal antibodies against pneumolysin to mice experimentally infected with the pneumococcus. Although immunotherapy was associated with a decrease in bacterial lung colonization and lower frequencies of tissue injury and bacteremia, it may be expensive and impractical in the clinical setting.

## 6. CONCLUSIONS

Bacteremic pneumococcal pneumonia continues to have major medical impact throughout the world. Much recent research has focused on optimal strategies for the management of this condition. Antimicrobial therapy is potentially compromised by emerging resistance of this microorganism to commonly used antibiotics. However, a greater understanding of PK/PD parameters, together with knowledge derived from various clinical studies, have allowed us choose suitable agents or combinations of agents, in appropriate dosages, that are most commonly associated with a better outcome. A number of adjunctive therapies have also been studied in an attempt to further reduce the high mortality of pneumococcal infections, of which the macrolides themselves, and possibly the corticosteroids appear to be the most promising. Much further research is still needed and is currently ongoing.

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## LEGENDS TO THE FIGURES

**Figure 1:** Time above MIC – correlation of serum pharmacokinetics with MIC (susceptibility) of an organism. Drug A is present at a concentration of 2 mg/L for 50% of the dosing interval, while drug B is present at a concentration of 2 mg/L for 30% of the dosing interval. Reproduced from Jacobs MR. Clin Microbiol Infect 2001; 7: 589-596, with permission.

**Figure 2:** AUC/MIC and peak/MIC ratio – correlation of serum pharmacokinetics with MCI (susceptibility) of an organism. The MIC at which the magnitudes of these ratios that are required for clinical success are achieved becomes the pharmacokinetic/pharmacodynamic breakpoint. Reproduced from Jacobs MR. Clin Microbiol Infect 2001; 7: 589-596, with permission.

**Figure 1**

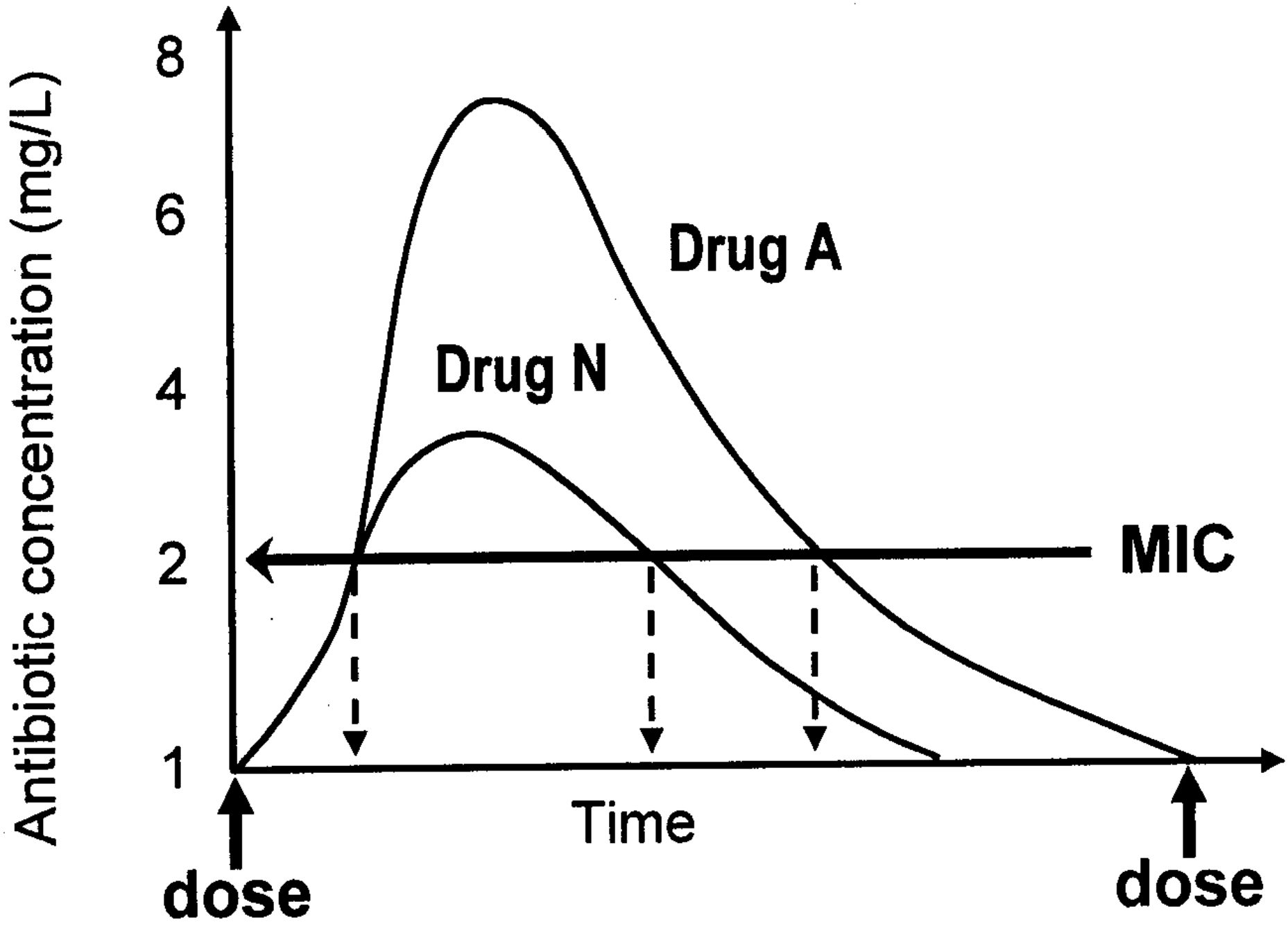
Antibiotic concentration (mg/L)
8
6
4
2
1
Drug A
Drug N
MIC
Time
dose
dose

**Figure 2**

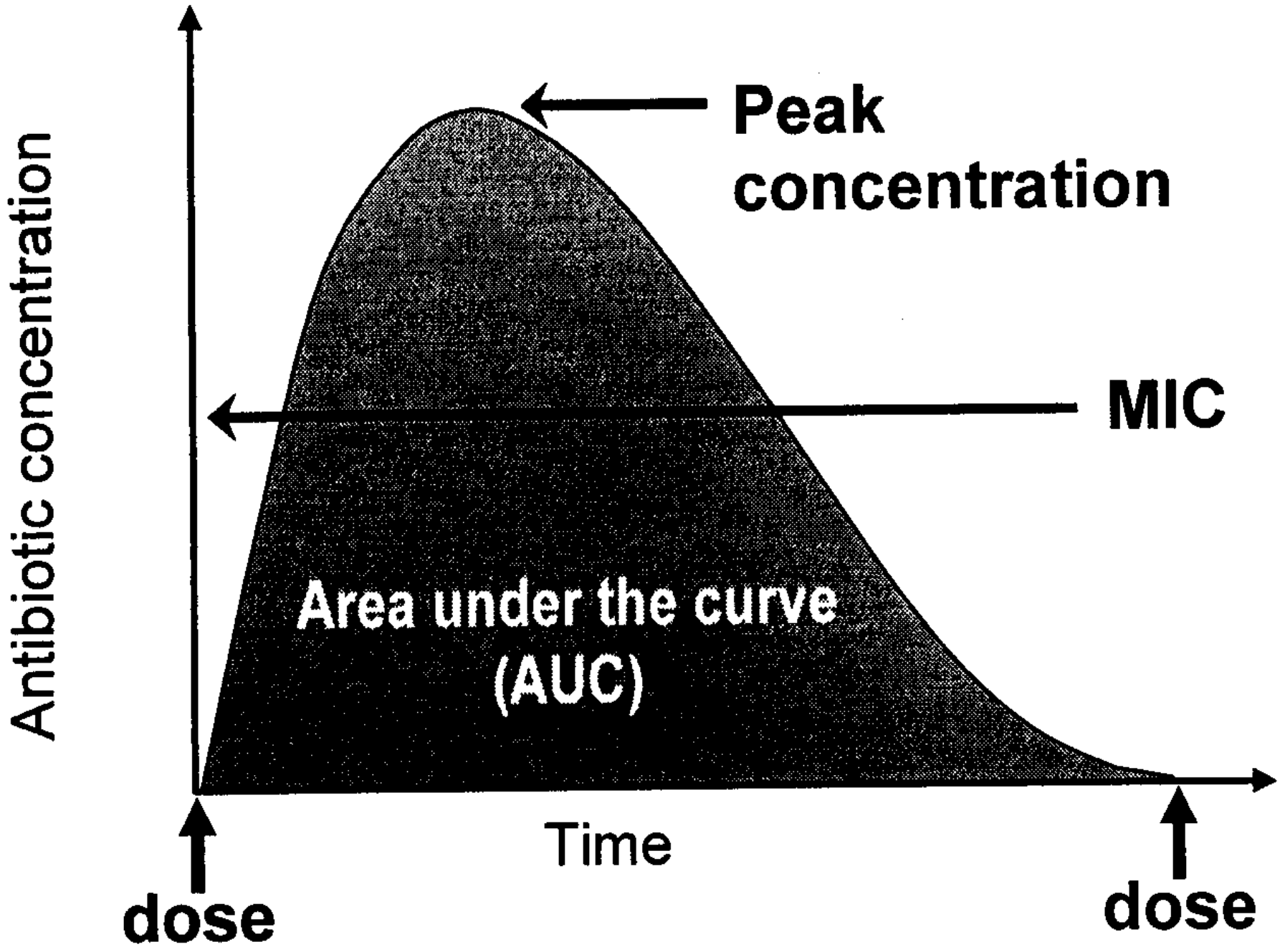
Antibiotic concentration
Peak concentration
MIC
Area under the curve (AUC)
Time
dose
dose

Table 1. Studies documenting the impact of combined antibiotic therapy on the outcome of pneumococcal pneumonia, predominantly in cases with pneumcoccal bacteremia.

| AUTHORS | YEAR | TYPE OF STUDY | DIAGNOSIS | PATIENT No. | END POINT |
|---|---|---|---|---|---|
| **Positive studies** | | | | | |
| Mufson and Stanek | 1999 | multicentre, surveillance | bacteraemic pneumococcal pneumonia | various | case fatality rate |
| Waterer *et al* | 2001 | multicentre, retrospective | bacteraemic pneumococcal pneumonia | 225 | hospital mortality |
| Martinez *et al* | 2003 | single centre, retrospective | bacteraemic pneumococcal pneumonia | 409 | in-hospital mortality |
| Baddour *et al* | 2004 | multinational, multicentre, prospective, observational | pneumococcal bacteraemia, predominantly pneumonia | 844 | 14- day mortality |
| Weiss et al | 2004 | single centre, retrospective | bacteraemic pneumococcal pneumonia | 95 | mortality rate |
| **Negative studies** | | | | | |
| Harbarth *et al* | 2005 | multicentre, retrospective | monobacterial pneumococcal sepsis (with or without bacteraemia) | 167 | case fatality rate |
| Dwyer *et al* | 2006 | multinational, multicentre prospective observational | bacteraemic pneumococcal pneumonia | 340 | case fatality rate |
| Aspa *et al* | 2006 | multicentre, prospective, observational | pneumococcal pneumonia (with or without bacteraemia) | 638 | 30- day mortality |
| Choksi *et al* | 2007 | multicentre, retrospective | bacteraemic pneumococcal pneumonia | 108 | in- hospital mortality |

Table 2: Possible mechanism(s) of benefit associated with the addition of a macrolide to standard β-lactam therapy in the management of patients with pneumococcal CAP

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- Cover for infections with 'atypical' pathogens
- Cover for polymicrobial infections
- Cover for infections with isolates demonstrating antimicrobial resistance or tolerance
- Synergistic effects, especially in immunocompromised patients
- Anti-inflammatory, immunomodulatory effects of the macrolide group of antibiotics

Reproduced from Feldman C, Anderson R. New insights into pneumococcal disease. Respirology 2009; 14: 167-179, with permission.

**Table III.** Pathogen- and host-directed anti-inflammatory activities of macrolides

| Target | Mechanism of anti-inflammatory action |
|---|---|
| Pathogen | Inhibition of the production of bacteria-derived, proinflammatory mediators (toxins, adhesins, biofilm, quorum sensors) |
| Structural cells of the host (epithelial cells, fibroblasts, airway smooth muscle cells) | Inhibition of cytokine/chemokine production, particularly interleukin-8 |
| Monocytes/macrophages | Inhibition of production of reactive oxidant species and cytokines/chemokines[a] |
| Neutrophils | Inhibition of the generation of reactive oxidant species and adhesion to vascular endothelium; induction of apoptosis[a] |

a Reviewed in Feldman and Anderson.[114]